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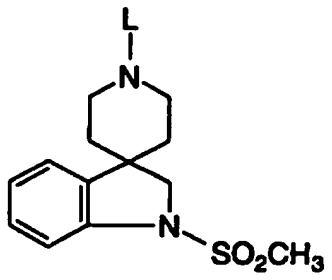
(54) Title: PROCESS FOR THE PREPARATION OF SPIROINDOLINES

(57) Abstract

The present invention is directed to a novel process for the preparation of a spiroindoline sulfonamides of formula (I), wherein L is hydrogen or an amino protecting group. These compounds are useful in the preparation of certain spiro compounds which have the ability to stimulate the release of natural or endogeneous growth hormone. The spiro compounds may be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food or wool production where the stimulation of growth hormone will result in a larger, more productive animal.



(I)

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TITLE OF THE INVENTION

PROCESS FOR THE PREPARATION OF SPIROINDOLINES

BACKGROUND OF THE INVENTION

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body: (1) Increased rate of protein synthesis in all cells of the body; (2) Decreased rate of carbohydrate utilization in cells of the body; (3) Increased mobilization of free fatty acids and use of fatty acids for energy. A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

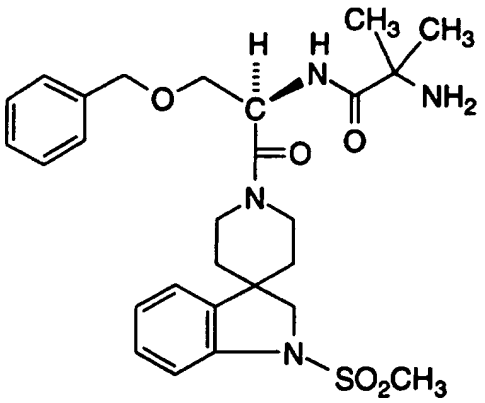
Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering GRF or a peptidal compound which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray. Other compounds have

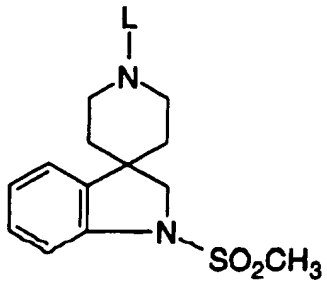
been developed which stimulate the release of endogenous growth hormone.

In particular, certain spiro compounds are disclosed in PCT Patent Publication WO 94/13696 as being non-peptidal growth hormone secretagogues. These compounds have the ability to stimulate the release of natural or endogenous growth hormone and thus may be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food or wool production where the stimulation of growth hormone will result in a larger, more productive animal.

Among the preferred compounds disclosed therein is spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyl-oxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate which has the structure:

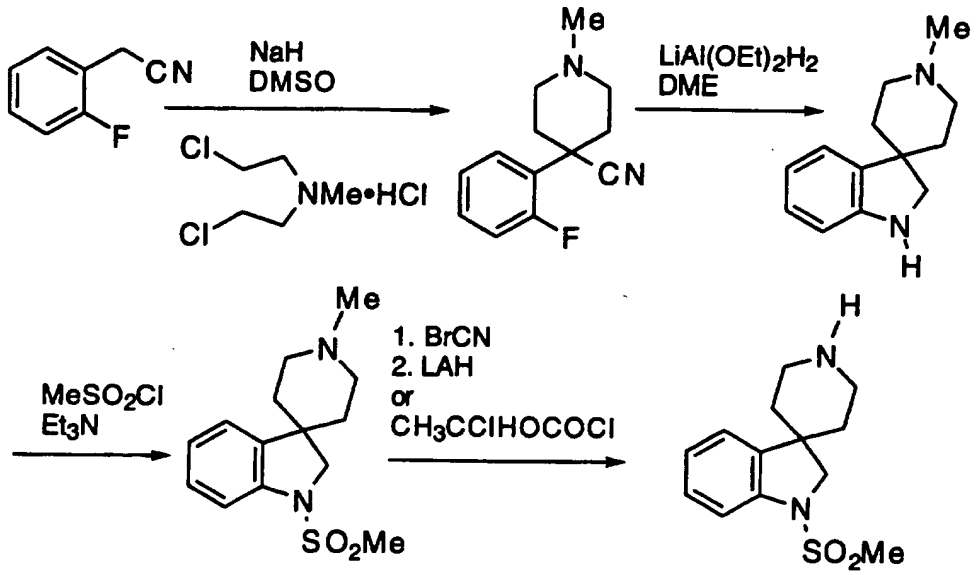


PCT Patent Publication WO 94/13696 discloses several methods for preparing these spiro compounds. Some of these methods employ as an intermediate the spiroindoline sulfonamide of the formula:



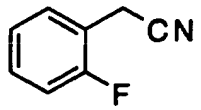
wherein L is hydrogen or an amino protecting group.

The known route to prepare this compund (wherein L is hydrogen) may be summarized as follows:

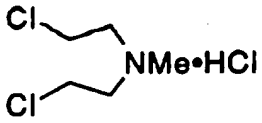


Regarding this route see: (a) Reeves, P.C.; Cammack, T.J. *Heterocyclic Chem.*, **1986**, *23*, 73-75; (b) Ong, H.H.; Agnew, N.M. *Heterocyclic Chem.*, **1981**, *18*, 815-820; (c) Ong, H.H; Proffit, J.A., Fortunato, J; Glamkowski, E.J.; Ellis, D.B.; Geyer, H.M.; Wilker, J.C.; Burghard, H. *J. Med. Chem.*, **1983**, *26*, 981-986; and (d) Bercz, C.V.; Rodney, D.I.; *J. Pharm. Sci.*, **1972**, *61*, 1316-1317.

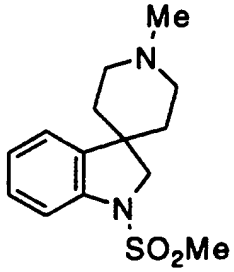
However, the route previously disclosed for the synthesis of this spiroindoline sulfonamide intermediate suffered from several disadvantages. In particular, the fluoroaromatic nitrile starting material of the formula:



is not readily available in larger quantities. In the first step of the sequence the bischloroethylmethylamine•HCl salt of the formula:

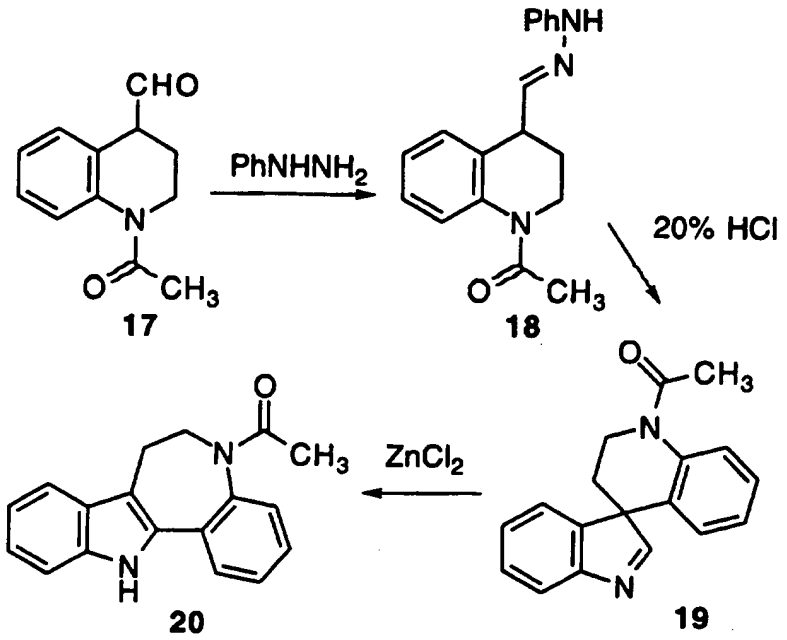


is highly toxic and carcinogenic, and the use of sodium hydride/DMSO at elevated temperatures is dangerous. The hydride reduction is hazardous due to the exothermic reaction needed to form the necessary reducing agent from the highly reactive pyrophoric lithium aluminum hydride and the prolonged period at elevated temperature to complete the reduction. In addition, the demethylation of the piperidine of the formula:

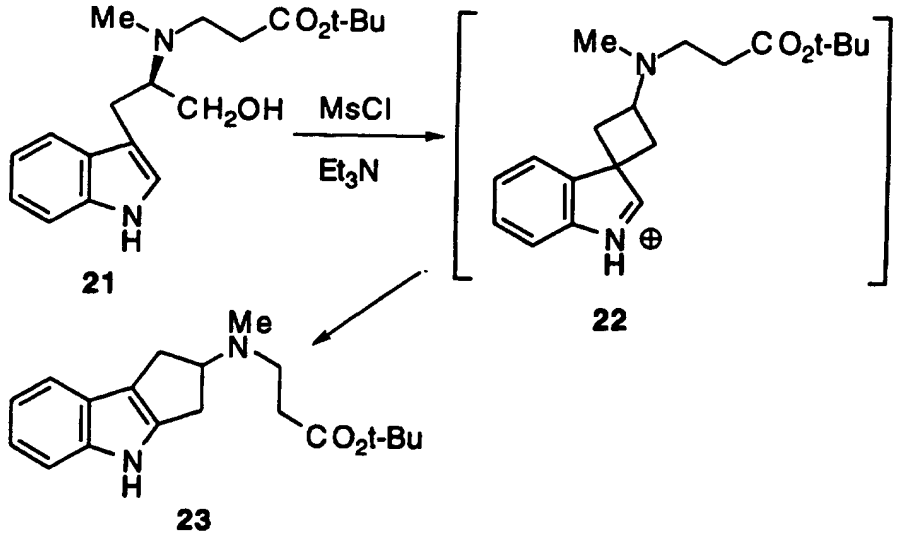


requires either the use of toxic cyanogen bromide followed by a reduction with reactive lithium aluminum hydride or the use of the supply limited and expensive chloroethyl chloroformate. Furthermore, this route required several chromatographic purifications. Accordingly, there is a need in the art for an improved process to prepare these spiroindoline sulfonamides.

The Ficher indole condensation of the tetrahydroquinoline-carboxaldehyde **17** with phenylhydrazine is known (Wang, T.S. *Tetrahedron Lett.* **1975**, 1637), but intermediate **19** readily undergoes the Wagner-Meerwein rearrangement to give the carbazole **20**.



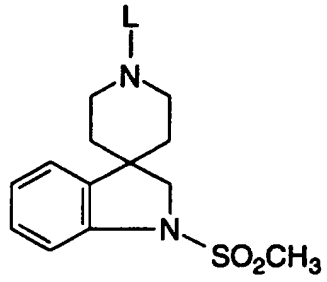
Another example of the ring-expanding reaction of spiroindolenines is the direct conversion of **21** to **23** via spiroindolenine **22** (Ganesan, A.; Heathcock, C.H. *Tetrahedron Lett.* **1993**, *34*, 439-440) as follows:



Additional references related to the use of the Fisher indole synthesis include: (a) Robinson, B. The Fischer Indole Synthesis; Wiley: New York, **1982**, e.g. 632-672; (b) Ungematch, F.; Cook, J.M. *Heterocycles*, **1978**, *9*, 1089-1119; (c) Wang, T.S.T. *Tetrahedron Lett..*, **1975**, *19*, 1637-1638; (d) Heacock, R.A.; Kasparek, S. The Indole Grignard Reagents. in vol 10 of *Advances in Heterocyclic Chemistry*; Katritsky, A.R.; Boulton, A.J. Eds.; Academic Press; New York, **1969**, 43-50; (e) Jackson, A.H.; Naidoo, B.; *Tetrahedron*, **1969**, *25*, 4843-4852; (f) Jackson, A.H.; Smith, A.E.; *Tetrahedron*, **1968**, *24*, 2227-2239; (g) Jackson, A.H.; Smith, P.; *Tetrahedron*, **1968**, *24*, 403-413; (h) Jackson, A.H.; Smith, A.E.; *Tetrahedron*, **1965**, *21*, 989-1000; and (i) Zinnes, H; *U.S. Patent No.* 3,892,766 (July 1, 1975).

SUMMARY OF THE INVENTION

The instant invention is directed to a process for the preparation of a spiroindoline sulfonamide compound of the formula:

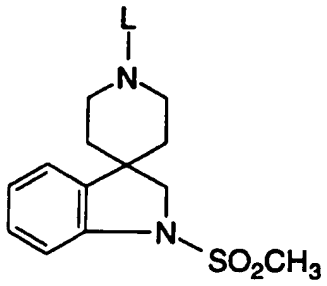


wherein L is hydrogen or an amino protecting group.

These spiroindoline sulfonamides may be used to prepare certain spiro compounds which have the ability to stimulate the release of natural or endogenous growth hormone. These spiro compounds may be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food or wool production where the stimulation of growth hormone will result in a larger, more productive animal.

DESCRIPTION OF THE INVENTION

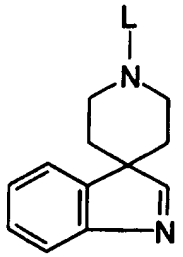
The present invention is directed to a novel process for the preparation of a spiroindoline sulfonamide compound of the formula:



wherein L is hydrogen or an amino protecting group.

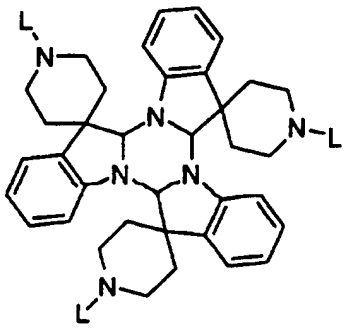
The instant process provides the desired spiroindoline sulfonamide from readily available inexpensive and environmentally acceptable starting materials reagents and solvents. The process does not use any chromatographic purifications, and it is possible to produce the spiroindoline sulfonamide without isolation of any of the intermediates.

In a key step of the instant process, a Fischer indole condensation provides the spiroindolenine of the formula:



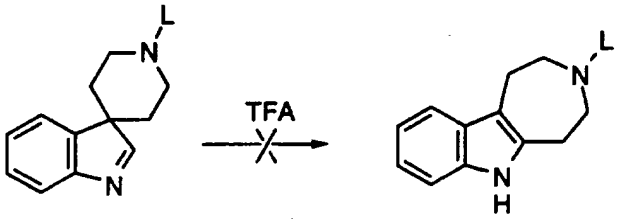
(wherein L is hydrogen or an amino protecting group) in virtually quantitative yield without any detectable Plancher rearrangement (Wagner-Meerwein rearrangement) to the carbazole. The Wagner-Meerwein rearrangement of a spiroindolenine to a carbazole is the reaction that is normally observed for 3,3-disubstituted spiroindolenines which do not have a substituent in the 2-position (see e.g. Jackson, A.H.; Smith, A.E.; *Tetrahedron,* **1968**, *24*, 2227-2239).

In solution, the spiroindolenine can exist in equilibrium with a cyclic trimer of the formula:



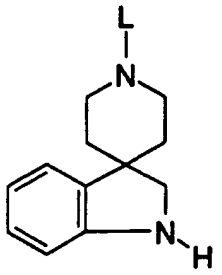
with the position of the equilibrium dependent upon the solvent and the pH.

An unexpected discovery in the instant invention is that there is no detectable tendency for either the spiroindolenine or its trimer to undergo a subsequent Wagner-Meerwein rearrangement to the ring expanded 2,3-disubstituted indole (depicted as follows)



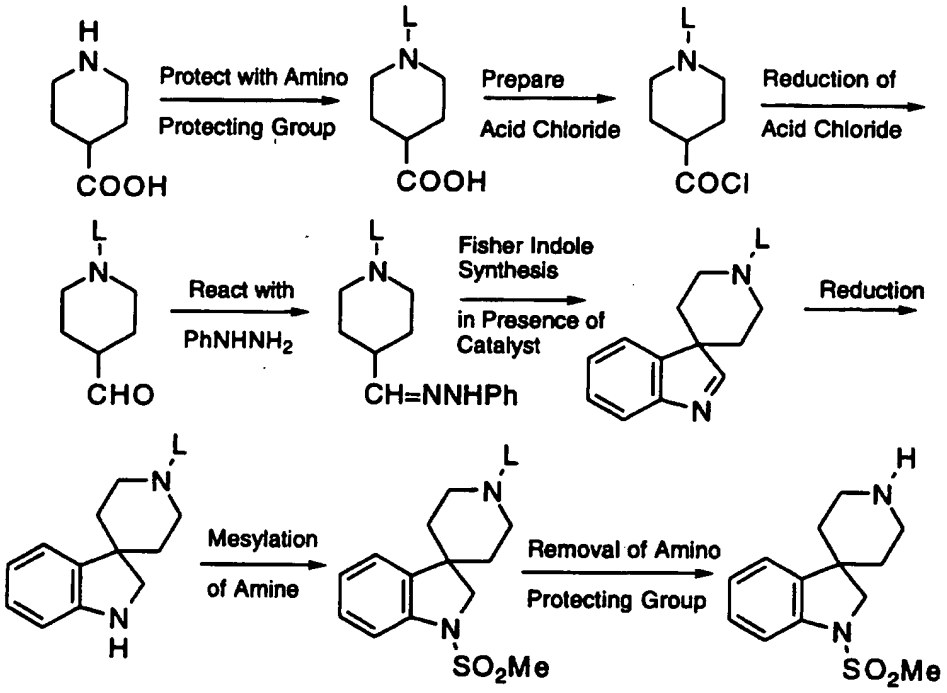
which is commonly observed for 3,3-disubstituted spiroindolenine compounds which do not have a substituent in the 2-position (see e.g. Jackson, A.H.; Smith, A.E.; *Tetrahedron,* **1968**, *24*, 2227-2239).

In a next step, the spiroindolenine is then reduced *in-situ* to the spiroindoline of the formula:

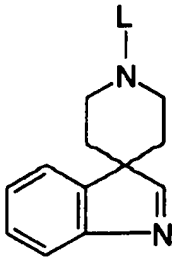


(wherein L is hydrogen or an amino protecting group) with an appropriate reducing agent, such as sodium borohydride or lithium borohydride, in the presence of an alcohol, such as methanol, ethanol, or isopropanol, thus avoiding any further manipulation of the spiroindolenine. This spiroindoline is then converted to the desired spiroindoline sulfonamide by straightforward mesylation.

The entire process may be summarized as follows:

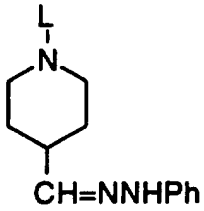


Within this general process, a key processes concerns the preparation of a compound of formula I:



I

wherein L is hydrogen or an amino protecting group, via a Fisher indole reaction which comprises reacting a compound of the formula:



in the presence of a catalytic agent, to give the compound of formula I.

Catalytic agents suitable for the Fischer indole reaction of the present invention are generally strong acids. Catalytic agents appropriate for this process include: trifluoroacetic acid; hydrogen fluoride; hydrogen chloride; hydrogen bromide; hydrogen iodide; chlorotrimethylsilane; trifluoromethanesulfonic acid; methanesulfonic acid; camphorsulfonic acid; sulfuric acid; phosphoric acid; and arylsulfonic acids, such as benzenesulfonic acid, p-toluenesulfonic acid, and p-chlorobenzene-sulfonic acid. Preferred catalytic agents include: trifluoroacetic acid; methanesulfonic acid; camphorsulfonic acid; benzenesulfonic acid, p-toluenesulfonic acid; and p-chlorobenzene-sulfonic acid. The most preferred catalytic agent is trifluoroacetic acid.

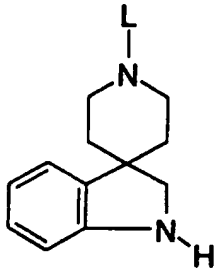
Solvents appropriate for this processes include: acetonitrile; propionitrile; chlorinated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, ortho-dichlorobenzene; benzene; toluene; xylenes; and the like; and mixtures

thereof. Preferred solvents include: dichloromethane; chloroform; mixtures of toluene-acetonitrile (4:1 to 100:1 v/v); mixtures of chlorobenzene-acetonitrile (4:1 to 100:1 v/v); and mixtures of ortho-dichlorobenzene-acetonitrile (4:1 to 100:1 v/v). The most preferred solvents include: dichloromethane; mixtures of toluene-acetonitrile (9:1 to 100:1 v/v); mixtures of chlorobenzene-acetonitrile (9:1 to 100:1 v/v); and mixtures of ortho-dichlorobenzene-acetonitrile (4:1 to 100:1 v/v).

The preferable reaction temperature range is between -40 and 150 °C, and the most preferable range is between 35 and 55°C.

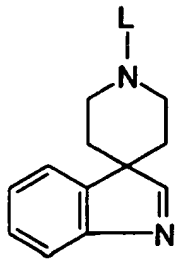
If the piperidine starting material is not protected (L is hydrogen) it is preferred that such compound be present as its acid addition salt, i.e. as a salt derived from using an inorganic or organic acid, such as hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methanesulfonic acid and the like.

Another process within this general process concerns the preparation of a compound of the formula II:



II

wherein L is hydrogen or an amino protecting group, which comprises reacting a compound of the formula I:



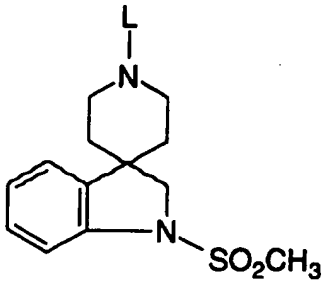
I

with a reducing agent optionally in the presence of an alcohol to give the compound of formula II.

In this process, reduction may be accomplished by use of a reducing agent, such as a hydride reducing agent or by catalytic reduction. Appropriate hydride reducing agents include sodium borohydride, lithium borohydride, lithium aluminum hydride, di-isobutylaluminum hydride, bis(2-methoxyethoxy)aluminum hydride, triacetoxy borohydride, borane or carboxylates thereof, and other reducing agents which are known in the art to reduce imines. For this reduction the preferred reducing agent is sodium borohydride or lithium borohydride. If sodium borohydride or lithium borohydride is employed as a reducing agent, it is prefered that the reduction is conducted in the presence of an alcohol, such as methanol, ethanol, or isopropanol.

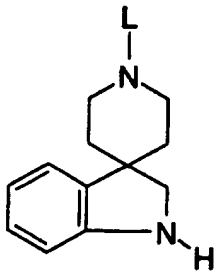
In the interest of efficiency, it is preferred that this reduction be conducted *in situ* without isolation of the compound of formula I following its preparation by the aforementioned process.

Another process within this general process concerns the preparation of a compound of the formula III:



III

wherein L is hydrogen or an amino protecting group, which comprises reacting a compound of the formula II:

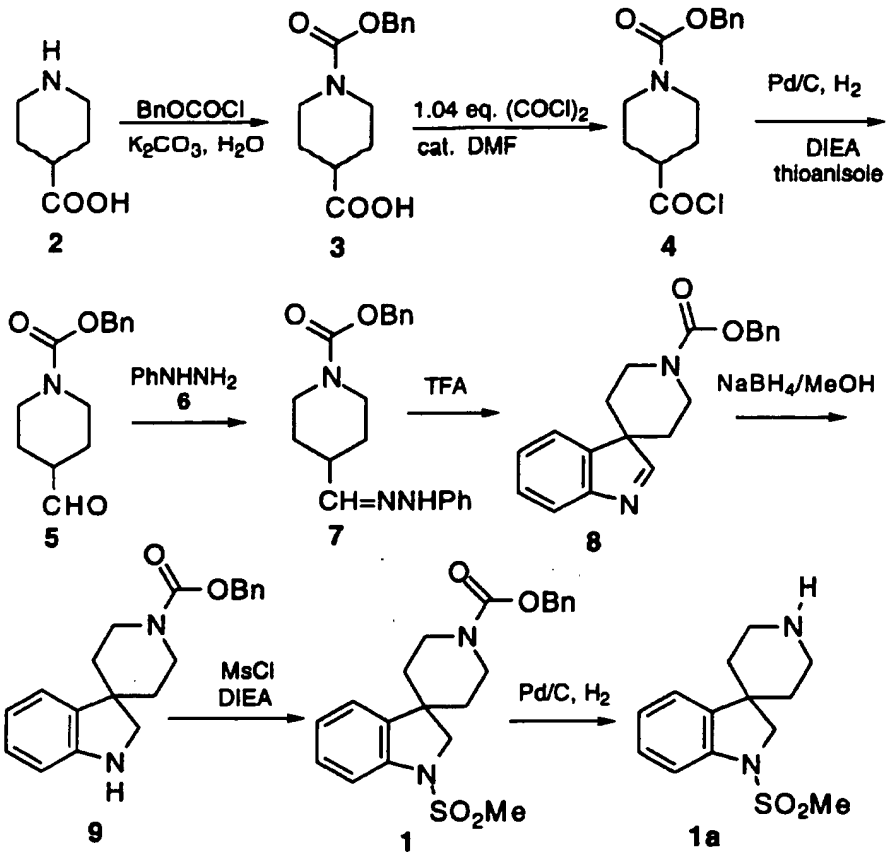


II

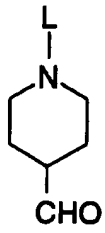
wherein L is hydrogen or an amino protecting group, with a sulfonylating agent to give the compound of formula III.

In this process, the introduction of the sulfonyl group may be accomplished by use of a sulfonylating agent, such as methanesulfonyl chloride, methanesulfonic anhydride, methanesulfonic acid in the presence of a suitable dehydrating agent, or various sulfonylating agents known in the art, in which methanesulfonyl chloride and methanesulfonic anhydride are preferred, and in which methanesulfonyl chloride is more preferred. This reaction is generally conducted in the presence of an amine base, such as di-isopropylethylamine, triethylamine, dimethylaminopyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene, or other amine bases known in the art, in which di-isopropylethylamine is preferred.

In a preferred embodiment of the present invention, the entire process may be outlined as follows:



In this preferred embodiment, the starting materials used in the Fischer indole condensation are: (1) a piperidine-4-carboxaldehyde {such as piperidine-4-carboxaldehyde or one of its acid addition salts, an N-protected piperidine-4-carboxaldehyde of the formula:



wherein L is a CBZ protecting group, an *N*-acetylpiperidine-4-carboxaldehyde, or another suitably *N*-protected piperidine-4-carboxaldehyde}; and (2) a phenylhydrazine (such as phenylhydrazine, 2,3, or 4-bromophenylhydrazine, 2,3, or 4-chloro-phenylhydrazine, or ar salt thereof). The *N*-protected piperidine carboxaldehydes are readily available from the corresponding piperidine carboxylic acids via acid chloride formation and Rosenmund reduction.

In the above structural formula and throughout the instant specification, the following terms have the indicated meanings:

The term "amino protecting group" is intended to indicate the presence of an appropriate protecting group for amino, such as those described in Greene, T.W., Wuts, P.G.M. Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Sons, Inc., New York, 1991. An appropriate protecting group will be able to withstand the reaction conditions of intermediate processes, prior to being removed when desired. Suitable protecting groups for amino include those groups well known in the art such as: benzyl, benzyloxymethyl, benzyloxycarbonyl (carbobenzyloxy), benzylsulfonyl, 2-bromoethyloxycarbonyl, t-butoxy-carbonyl, 2-chloro-benzyloxycarbonyl, 2-chloroethyloxycarbonyl, di-t-amyloxycarbonyl, 9-fluoroenylmethyloxycarbonyl, isopropoxycarbonyl, 4-methoxy-benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrophenyl-sulfonyl, phthaloyl, 2,2,2-trichloro-t-butyloxycarbonyl, trifluoroacetyl,

tirphenylmethane, and vinyloxycarbonyl groups, and the like, in which the preferred ones include benzyloxycarbonyl (carbobenzyloxy), 2-chlorobenzyloxy-carbonyl, 4-methoxybenzyloxycarbonyl, and 4-nitrobenzyloxycarbonyl groups, and in which the most preferred one is the benzyloxycarbonyl (carbobenzyloxy) group.

If L is an amino protecting group, it may be removed using well known procedures (Greene, T.W., Wuts, P.G.M. Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Sons, Inc., New York, 1991). Removal of benzyloxycarbonyl (carbobenzyloxy) groups may be achieved by a number of methods known in the art; for example, catalytic hydrogenation with hydrogen in the presence of a noble metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of benzyloxycarbonyl (carbobenzyloxy) groups may also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide. Removal of t-butoxycarbonyl protecting groups may be carried out in a solvent such as methylene chloride or methanol or ethyl acetate, with a strong acid, such as trifluoroacetic acid or hydrochloric acid or hydrogen chloride gas.

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration and if two carbon atoms or more they may include a double or a triple bond. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, allyl, propargyl, and the like .

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, and the like.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine, and iodine.

The term "aryl" within the present invention, unless otherwise specified, is intended to include aromatic rings, such as carbocyclic and heterocyclic aromatic rings selected the group consisting of: phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrrazinyl, or isothiazolyl, which may be optionally substituted by 1 to 3 of C_1-C_6 alkyl, 1 to 3 of halogen, 1 to 2 of $-OR^2$, methylenedioxy, $-S(O)_mR^2$, 1 to 2 of $-CF_3$, $-OCF_3$, nitro, $-N(R^2)C(O)(R^2)$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, -1H-tetrazol-5-yl, $-SO_2N(R^2)(R^2)$, $-N(R^2)SO_2$ phenyl, or $-N(R^2)SO_2R^2$, wherein R^2 is selected from: hydrogen, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring, optionally including oxygen, sulfur or NR^{3a}, where R^{3a} is hydrogen, or C_1-C_6 alkyl, optionally substituted by hydroxyl.

Throughout the instant application, the following abbreviations are used with the following meanings:

Bu	butyl
Bn	benzyl
BOC, Boc	t-butyloxycarbonyl
BOP	Benzotriazol-1-yloxy tris/dimethylamino)-phosphonium hexafluorophosphate
calc.	calculated
CBZ, Cbz	Benzyloxycarbonyl
DCC	Dicyclohexylcarbodiimide
DIEA	Di-isopropylethylamine
DMF	N,N-dimethylformamide
DMAP	4-Dimethylaminopyridine
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride
EI-MS	Electron ion-mass spectroscopy
Et	ethyl

eq.	equivalent(s)
FAB-MS	Fast atom bombardment-mass spectroscopy
h, hr.	hours
HOBT, HOBt	Hydroxybenztriazole
HPLC	High pressure liquid chromatography
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LHMDS	Lithium bis(trimethylsilyl)amide
Me	methyl
MF	Molecular formula
MHz	Megahertz
MPLC	Medium pressure liquid chromatography
NMM	N-Methylmorpholine
NMR	Nuclear Magnetic Resonance
Ph	phenyl
Pr	propyl
prep.	prepared
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane

The amine compounds employed as starting materials for the process of the present invention may be present as their acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methane sulfonic and the like. Similarly the compounds produced by the processes of the instant invention may be isolated in the form of their pharmaceutically acceptable acid addition salts. In addition, certain compounds containing an acidic function such as a carboxy can be in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

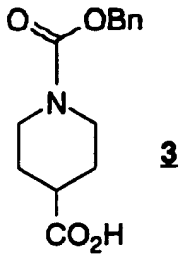
The preparation of compounds with the process of the present invention may be carried out in sequential or convergent synthetic routes. It is noted that in some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. In general, the process of the present invention is conducted in a sequential manner as presented herein.

The phrase "standard peptide coupling reaction conditions" as used herein is intended to mean the coupling of a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in a inert solvent such as dichloromethane in the presence of a catalyst such as HOBT. The uses of protective groups for amine and carboxylic acid to facilitate the desired reaction and minimize undesired reactions are well documented. Conditions required to remove protecting groups which may be present and can be found in Greene, T, and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY 1991. CBZ and BOC may be used extensively in the instant process, and conditions for their removal are known to those skilled in the art. For example, removal of CBZ groups may be achieved by a number of methods known in the art; for example, catalytic hydrogenation with hydrogen in the presence of a nobel metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of CBZ groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide. Removal of BOC protecting groups is carried out in a solvent such as methylene chloride or methanol or ethyl acetate, with a strong acid, such as trifluoroacetic acid or hydrochloric acid or hydrogen chloride gas.

Many of the starting materials are either commercially available or known in the literature and others can be prepared following literature methods described for analogous compounds. The skills required in carrying out the reaction and purification of the resulting reaction products are known to those in the art. Purification procedures include crystallization, normal phase or reverse phase chromatography.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

EXAMPLE 1



3

Isonipecotic acid-*N*-benzyl carbamate (**3**)

Materials:

Isonipecotic acid (**2**) T.C.I.	4.02 kg (31.1 mol)
Benzyl chloroformate (Schweitzerhall)	6.91 kg (40.5 mol)
K_2CO_3	10.1 kg (72.9 mol)
Water	40.2 L

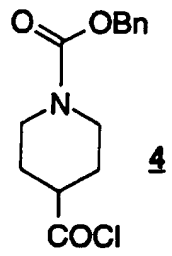
Isonipecotic acid (**2**) and K_2CO_3 were dissolved in 40.2 L of water in a 100 L 4 neck flask with mechanical stirring under N_2 and the solution was cooled to 10 °C. Benzyl chloroformate was added, maintaining the temperature between 9 and 14 °C, and the mixture was warmed up to 22 °C after the addition was complete and aged for 58 h.The addition was completed in 4 h at which point the pH was 9.0. After aging for 58 h there was no change in the pH.

The reaction mixture was transferred to a 200 L extractor and washed with 3 × 13 kg (15 L) of IPAC and 1 × 12 L of EtOAc. The aqueous layer was extracted with 8 L of toluene.After the washes the benzyl alcohol content was reduced from 3.8% to 1.4% by HPLC analysis. HPLC analytical: Dupont Zorbax 25 cm RXC8 column with 1.5 mL/min flow and detection at 254 nm; isocratic mixture with 35%

MeCN, 65% of 0.1% aqueous H_3PO_4; retention times: 3 = 6.9 min, benzyl alcohol = 3.3 min, toluene = 17.3 min.

The aqueous phase was acidified with of 37% aqueous HCl to pH 1.8. Carbon dioxide was evolved during the addition of HCl, but gas evolution was easily controlled. The addition of HCl took <1 h and required 10 L of conc. HCl. The aqueous phase was extracted with 3 × 66 L of toluene. The toluene extracts were dried with 2 kg of sodium sulfate and filtered through a pad of Solka-floc. The combined filtrates weighed 17.8 kg. The crude yield of carbamate **3** was 7.89 kg (97%) (as obtained by evaporation of weighed aliquots of the filtrates to dryness). The filtrates were transferred through a 10 μ inline filter to a 100 L flask. The extracts were concentrated at 10 mbar at <25 °C to a volume of 18 L.The final concentration of carbamate **3** was 440 g/L. The concentration of the toluene filtrate served to azeotropically remove final traces of water (final KF = 170mg/L). The product was 99.1 area % pure with 0.9 area % benzyl alcohol as the only impurity.

EXAMPLE 2



4

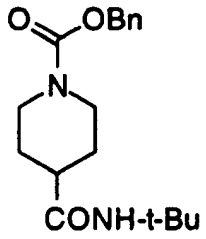
Isonipecotic acid chloride-*N*-benzyl carbamate (**4**)

Materials:

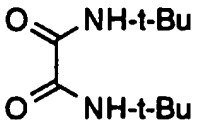
Isonipecotic acid *N*-benzyl carbamate (**3**) in toluene. (MW = 263.30)	7.89 kg (30.0 mol) in 17.9 L
Oxalyl chloride (MW = 126.93)	3.94 kg (31.0 mol)
DMF (MW = 73.10)	10 mL
Toluene	12 L

To the toluene solution of benzyl carbamate **3** from the preceding step was added 5 mL of DMF and 10 L of toluene. The oxalyl chloride was added over a period of 20 min. The reaction mixture was aged for 16 h at 18 °C under a slow stream of nitrogen.HPLC analysis of the reaction mixture showed that 1.3% of the carboxylic acid **3** still remained unreacted. The reaction mixture was warmed to 26 °C, and 5 mL of DMF were added. The mixture was aged for 2.5 h.

A 1.0 mL aliquot of the reaction mixture was quenched with 5.0 mL of tert-butylamine and analyzed after evaporation by HPLC: 25 cm Dupont Zorbax RXC8 column at 50 °C with 1 mL/min flow and detection at 220 nm; isocratic 42% MeCN, 58% of 0.1% aqueous H_3PO_4. This method showed that <0.05% of the acid **3** remained (as judged by **A**) and showed >3 area % **B** (>1 mol% $(COCl)_2$).



A



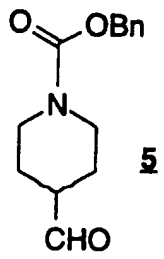
B

The mixture was concentrated at 10 mbar and a temperature of 20-25 °C until 5 L of solvent had been removed.

The typical HPLC profile of concentrated toluene solution after t-$BuNH_2$ quench described above is as follows:

Retention time (min)	Area %	Identity
2.1	<0.5%	carboxylic acid **3**
7.8	<0.5%	benzyl chloride
11.0	>99%	Cbz-t-butylcarboxamide **A**
12.1	NA	toluene
12.7	<0.5%	ditert-butyloxamide **B**

EXAMPLE 3



5

Piperidine-4-carboxaldehyde-1-benzyl carbamate (**5**)

Materials:

Isonipecotic acid chloride *N*-benzyl carbamate (**4**)	3.38 kg (12.0 mol)
in toluene (MW = 281.74)	in 5.54 kg
DIEA (KF = 18 mg/L)	1.55 kg (15.0 mol)
10% Pd/C (KF < 20 mg/g)	101 g
thioanisole (MW = 124.21, d = 1.058)	0.56 g

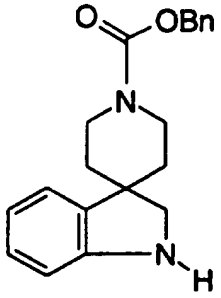
The DIEA and thioanisole were added to the solution of (**4**) in toluene from the previous step and the catalyst was suspended in this mixture. The mixture was immediately placed into the 5 gal autoclave and hydrogenated at 20 °C and 40 psi of H_2. After 18 h the reaction had taken up 70% the theoretical amount of hydrogen and HPLC analysis of an aliquot that was quenched with tert-butylamine indicated that 14.2 area % of acid chloride **2** remained. HPLC conditions same as above. Retention time: **3** = 8.1 min.

A second charge of catalyst (101 g) and thioanisole (0.54 g) were added as a slurry in 1375 mL toluene to the hydrogenator. After 23 h HPLC analysis of an aliquot that was quenched with tert-butylamine indicated that 1.8 area % of acid chloride **2** remained. The mixture was purged with nitrogen and the catalyst and precipitated DIEA•HCl were removed by filtration through Solka-floc. The filter cake was washed with 10 L of toluene. The filtrates were transferred through a 10 μ inline filter to a 50 L extractor and washed 2 × 7.2 L of 1 M aqueous HCl and 2 × 7.2 L of water. The mixture was concentrated at 10 mbar and a temperature of 25-30 °C until 5 L of residue remained.

Retention time (min)	Area %	Identity
2.1	<2	carboxylic acid **3**
6.6	<1	dimer **21**
8.1	>95	aldehyde **5**

The assay yield of aldehyde **3** was 94% by HPLC analysis.

EXAMPLE 4



9

CBZ-Spiroindoline (**9**)

Materials:

Piperidine-4-carboxaldehyde-1-benzyl carbamate (**5**) in toluene solution	1.71 kg (6.89 mol) in 21.4 kg
Phenylhydrazine	900 mL, 981 g (9.15 mol)
Trifluoroacetic acid (TFA)	2.20 L, 3.26 kg (28.6 mol)
$NaBH_4$	300 g, (7.93 mol)
Toluene	34.4 kg
MeCN	7.0 L
MeOH	7.0 L

The crude aldehyde **5** solution from the previous step was transferred through a 10 μ inline filter to a 100 L reactor equipped with Teflon coated copper coils for cooling or heating and a mechanical stirrer. Toluene (34.4 kg) and MeCN (7 L) were added, and the resulting solution was cooled to 0 °C. Phenylhydrazine was added in portions and the

temperature was maintained at -1 to 3 °C while nitrogen was continuously bubbled through the reaction mixture.

The phenylhydrazine was added until TLC and HPLC analysis indicated complete consumption of the aldehyde **5** and the appearance of a slight excess (<5%) of phenylhydrazine. TLC conditions: Silica, E. Merck Kieselgel G60 F254 0.25 mm; diethyl ether/pentane (4/1); and developing agent 0.5% ceric sulfate, 14% ammonium molybdate in 10% aqueous sulfuric acid then heat; R_f: aldehyde **5** = 0.52, phenylhydrazone **7** = 0.61, phenylhydrazine **6** = 0.21. HPLC conditions: 25 cm Dupont Zorbax RXC8 column at 30 °C with 1.0 mL/min flow and detection at 254 nm; gradient schedule:

Time (min)	acetonitrile:water
0	57:43
10	65:35
15	75:25
18	75:25

retention times: phenylhydrazine **6** = 4.5 min, toluene = 7.2 min, phenylhydrazone **7** = 11.4 min.

The reaction mixture was aged for 30 min at 0-2°C, and TFA was added maintaining the temperature between 2 and 7°C. The reaction mixture was warmed to 50°C over 30 min, and maintained for 17 h. The nitrogen sparge through the reaction mixture was stopped and a slow stream of nitrogen was maintained over the reaction mixture. During the first hour at 5 °C the color gradually darkened to a deep green, and a relatively small amount of a white crystalline precipitate (ammonium trifluoroacetate) formed. After 17 h HPLC analysis (same conditions as above) indicated that the reaction mixture contained 91.6 area % indolenine **8** and 1.5% of unreacted phenylhydrazone remained. Aging the mixture for longer periods of time the did not increase the assay yield of indolenine **8**.

The reaction mixture was cooled to 12 °C, and 7.0 L of MeOH was added. $NaBH_4$ was added in small (<20 g) portions maintaining the temperature below 15 °C. The addition took 30 min.

Moderate hydrogen evolution was observed during the addition, but it was easily controlled and there was virtually no frothing. Near the end of the addition the color rapidly changed from green to brown and then bright orange. A small amount (<200 mL) of a heavier phase had separated (presumably aqueous salts). HPLC analysis (conditions as before) indicated that all of the indolenine **8** had been consumed (90.4 area % CBZ-indoline **9**); retention times: indolenine **8** = 7.5 min, indoline **9** = 8.2 min. TLC: ethyl ether as solvent, ceric sulfate-ammonium molybdate stain or 1% anisaldehyde stain; retention factors: indolenine **8** = 0.18, CBZ-indoline **9** = 0.33.

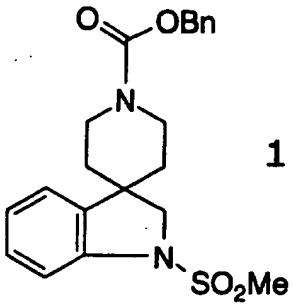
The color change from green to orange corresponds very closely to reaction end point. The quantity of $NaBH_4$ required to complete the reaction is heavily dependent on the temperature and rate of addition of $NaBH_4$, but the yield and quality of the product is virtually unaffected provided that the reaction is complete. The reaction mixture was cooled to 5 °C over a period of 30 min. Then 8 L of 3% aqueous NH_4OH (8 L) were added to bring the pH of the aqueous phase to 7.4, the mixture was agitated, and allowed to settle.The temperature rose to 15 °C.The cloudy yellow lower aqueous phase was separated. The organic phase was washed with 4 L of 3% aqueous NH_4OH, 2 × 4 L of water, and 2 × 4 L of brine. The weight of the organic phase after the washings was 53.5 kg, and the assay yield was 94%.

The washed toluene solution was combined with the washed organic phases of two other similarly processed reactions. The total aldehyde used in the three reactions was 5.06 kg, (20.5 mol). The total weight of CBZ-indoline **9** assayed in the combined organic phases was 5.91 kg, (18.3 mol, 90% assay yield). The combined organic phases were dried with 5 kg of sodium sulfate, treated with 250 g of Darco G60 carbon for 30 min, and filtered through Solka-floc. The filtrates were vacuum concentrated at 10 mbar at <25 °C until the residue was near dryness. The solvent switch was completed by slowly bleeding in 30 L of IPAC and reconcentrating to 14 L at 200 mbar at 50-60 °C. The mixture was heated to reflux in order to obtain a clear homogeneous

deep orange solution. ^{1}H NMR analysis indicated that the solution contained ca. 6 mol% of residual toluene after solvent switch.

The solution was cooled to 68 °C and seeded with 4 g of crystalline CBZ-indoline **9**. The solution was allowed to gradually cool to 26 °C over 6 h and aged for 9 h at 20-26 °C. The slurry was cooled to 2 °C over 1 h and aged at 2 °C for 1h. The product was isolated by filtration, and the filter cake was washed 2 × 2 L of 5 °C IPAC and 2 × 2 L of 5 °C MTBE. The product was dried in the vacuum oven at 30 °C under a nitrogen bleed to give 4.37 kg (74%) of the title compound **9** as a light tan crystalline powder. HPLC analysis of the product indicated 99.5 area % purity. The mother liquor (11 L) and the washes contained 1.15 kg (19%) of additional product **9** and ca 3% of Cbz-isonipecotic acid phenylhydrazide (retention time = 4.8 min).

EXAMPLE 5



1

CBZ-Spiroindoline-methanesulfonamide (**1**)

Materials:

CBZ-Spiroindoline (**9**)	1.69 kg (5.23 mol)
Methanesulfonyl chloride	599 g (5.23 mol)
Et3N (KF = 151)	635 g (6.27 mol)
THF (KF = 41)	12 L

A 22 L flask was charged with the solid CBZ-spiroindoline **9** and then 11.5 L of THF and the Et3N were transferred into the flask through a 10 μ inline filter. The resulting homogenous solution was cooled to 0 °C. A 1 L dropping funnel was charged with the

methanesulfonyl chloride and 500 mL of THF. The solution of the MsCl in THF was added to the reaction mixture maintaining the temperature between 0 and 4 °C.The addition took 5 h and was exothermic. A white precipitate, presumably triethylammonium hydrochloride formed during the addition. HPLC analysis indicated that the reaction was complete at the end of the addition (**9** was undetectable).

HPLC conditions: 25 cm Dupont Zorbax RXC8 column with 1.5 mL/min flow and detection at 254 nm. Gradient Schedule:

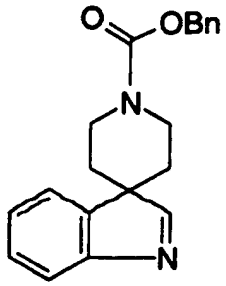
Time (min)	0.1% aq. H_3PO_4:MeCN
0	70:30
3	70:30
12	20:80
25	20:80

Retention times: **9** = 7.6 min, **1** = 13.6 min.

After the addition was complete the reaction mixture was warmed to 18 °C and aged for 16 h. There was no change in the appearance of the reaction mixture, and HPLC profile between the end of the addition and after the 16 h age. The reaction mixture was slowly transferred over 1h into a vigorously stirred solution of 30 L of water and 200 mL of 37% aqueous HCl in a 50 L flask. The temperature in the 50 L flask rose from 22 to 28 °C. The product separated as a pale tan gummy solid which changed to a granular solid. The aqueous suspension was cooled to 22 °C and aged for 1 h. The suspension was filtered, and the filter cake was washed with 2 × 4 L of MeOH/water (50/50). HPLC analysis indicated that <0.1% of the CBZ-Spiroindoline-methanesulfonamide**1** was in the mother liquors.

The filter cake was washed with 4 L of MeOH/water (50/50) to which 50 mL of 28% aqueous NH_4OH had been added. The filter cake was washed with 2 × 4 L of MeOH/water (50/50), and the solid was dried in the vacuum oven at 50 °C under a nitrogen bleed to give 2.03 kg (97%) of the title product **1** as an off-white powder. HPLC analysis of the solids indicated 93.7 area % **1**.

EXAMPLE 6



8

Optional Procedure for Isolation of Intermediate CBZ-Spiroindolenine (8)

Materials:

Piperidine-4-carboxaldehyde-1-benzyl carbamate (5)	12.37 g (0.050 mol)
Phenylhydrazine	5.41 g (0.050 mol)
Trifluoroacetic acid (TFA)	11.56 mL,17.10 g (0.150 mol)
Methylenechloride	500 mL

The CBZ-aldehyde 5 was dissolved in dichloromethane in a 1 L flask equipped with Teflon coated magnetic stirring bar. The resulting solution was cooled to 0 °C. Phenylhydrazine was added via a weighed syringe over 5 min and the temperature was maintained at -1 to 3 °C while nitrogen was continuously bubbled through the reaction mixture.

TLC and HPLC analysis indicated complete consumption of the CBZ-aldehyde 5 and the appearance of a slight excess (<2%) of phenylhydrazine. TLC conditions: Silica, E. Merck Kieselgel G60 F254 0.25 mm; diethyl ether/pentane (4/1); and developing agent 0.5% ceric sulfate, 14% ammonium molybdate in 10% aqueous sulfuric acid then heat; Rf: aldehyde 5 = 0.52, phenylhydrazone 7 = 0.61, phenylhydrazine 6 = 0.21. HPLC conditions: 25 cm Dupont Zorbax RXC8 column at 30 °C with 1.0 mL/min flow and detection at 254 nm; gradient schedule:

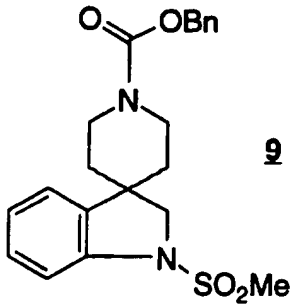
Time (min)	acetonitrile:water

0	57:43
10	65:35
15	75:25
18	75:25

retention times: phenylhydrazine **6** = 4.5 min, toluene = 7.2 min, phenylhydrazone **7** = 11.4 min.

The reaction mixture was aged for 10 min at 0-2 °C, and TFA was added by syringe maintaining the temperature between 2 and 7 °C.The reaction mixture was warmed to 35 °C over 30 min, and maintained for 17 h. The nitrogen sparge through the reaction mixture was stopped and a slow stream of nitrogen was maintained over the reaction mixture. During the first hour at 35 °C the color gradually darkened to a rosy pink then to a deep green, and a relatively small amount of a white crystalline precipitate (ammonium trifluoroacetate) formed. After 17 h HPLC analysis (same conditions as above) indicated that the reaction mixture contained 93 area % indolenine **8** and <0.5% of unreacted phenylhydrazone remained. Aging the mixture for longer periods of time the did not increase the assay yield of indolenine **8**. The reaction mixture was cooled to 10 °C, and a mixture containing 60 mL 28-30% ammonium hydroxide, 90 mL water and 150 g crushed ice was added with good stirring. The mixture changed to a salmon color. The organic phase was separated and washed twice with 400 mL water then 100 mL saturated aqueous NaCl. The organic phase was dried over magnesium sulfate and filtered through a plug of 5 g of silica. The filtrate was evaporated to give 15.84 g (99%) of indolenine **8** as a pale orange oil.

EXAMPLE 7



9

Procedure for the Preparation of CBZ-Spiroindoline-methanesulfonamide (1) without Isolation of Intermediate CBZ-Spiroindoline (9)

Step 1: CBZ-Spiroindoline (9)

Materials:

Piperidine-4-carboxaldehyde-1-benzyl carbamate (5)	49.5 g (0.20 mol)
Phenylhydrazine (Aldrich)	23.7 g (0.22 mol)
Trifluoroacetic acid (TFA)	75.4 g (0.66 mol)
Toluene (KF < 250 mg/L)	654 mL
MeCN (KF < 250 mg/L)	13.3 mL
$NaBH_4$	11.3 g, (0.30 mol)
Toluene	20 mL
MeOH	50 mL

A 2% (by volume) solution of MeCN in toluene was made up using 654 mL of toluene and 13.3 mL of MeCN. In a 2 L 3 neck flask equipped with a mechanical stirrer 617 ml of the above solution were degassed by passing a fine stream of nitrogen through the solution for 5 min. Phenylhydrazine and TFA were added to the mixture while still degassing.

The CBZ-aldehyde 5 was dissolved in the rest of the solution prepared above (50 mL) and degassed by bubbling nitrogen through the solution while in the addition funnel. The solution in the flask was heated

to 35 °C, and the aldehyde solution was slowly added to the phenylhydrazine-TFA over 2 h. The mixture was aged at 35 °C for 16 h.

HPLC conditions: 25 cm Dupont Zorbax RXC8 column at 50 °C with 1 mL/min flow and detection at 220 nm; isocratic 55% MeCN, 45% of 0.1% aqueous H_3PO_4. Typical HPLC profile after 16 h age:

Retention time (min)	Area %	Identity
1.6	0.1-0.5	phenylhydrazine **6**
4.1	<0.1	dimer **21**
4.7	<0.1	aldehyde **5**
5.0	NA	spiroindoline **9**
6.3	NA	toluene
6.9	97	spiroindolenine **8**
10.3	<0.2	phenylhydrazone **7**
	2-3 tot.	other impurities <0.2% ea.

The mixture was cooled to -10 °C and MeOH was added. A suspension of sodium borohydride in 20 mL toluene was added in small portions (1 mL) over 30 min taking care that the temperature did not exceed -2 °C.

Area %	Identity
0.1-1	phenylhydrazine **6**
85-90	CBZ-spiroindoline **9**
<0.1	CBZ-spiroindolenine **8**
10-15 tot.	other impurities (<3% ea.)

The temperature was raised to 10 °C over 1h, and 6% aqueous ammonia (200 mL) was added. The mixture was agitated for 10 min, allowed to settle for another 10 min, and the lower aqueous phase was drawn off. Acetonitrile (20 mL) and MeOH (20 mL) were added to the organic phase and it was washed with 150 mL of 15% brine.The organic phase was found to contain a 92% assay yield of CBZ-spiroindoline **9**.

Step 2: CBZ-Spiroindoline-methanesulfonamide (**1**)

Materials:

CBZ-Spiroindoline (**9**) (MW = 322.51)	(0.184 mol)
Methanesulfonyl chloride	21.1 g (0.184 mol)
DIEA (KF = 150 mg/L)	29.7 g, 40.1 mL (0.230 mol)
THF (KF = 41 mg/L)	150 mL

The crude solution of CBZ-spiroindoline **9** solution from Step 1 above was concentrated in a 1L 3 neck flask (60-70 °C, 150-200 Torr) till 250 g of residue remained. The THF and Et_3N were added, and the resulting homogenous solution was cooled to 0 °C. A 125 mL dropping funnel was charged with the methanesulfonyl chloride and 50 mL of THF. The solution of MsCl in THF was added over 2 h to the reaction mixture maintaining the temperature between 0 and 4 °C and aged for 2 h at 5-8 °C. The was slightly exothermic. A white precipitate, presumably DIEA-hydrochloride formed during the addition. HPLC conditions were the same as above. HPLC analysis indicated that the reaction was complete 1 h after the end of the addition (**9** was undetectable) and the assay yield was 94% from **9**. Retention time: **1** = 7.8 min. Typical HPLC profile of reaction mixture after 2 h age:

Area %	Identity
<0.1	CBZ-spiroindoline **9**
90-92	CBZ-sulfonamide **1**
8-10 tot.	other impurities (<2% ea.)

The mixture was warmed to 20 °C, and 200 mL of 1M aqueous HCl was added. The mixture was warmed to 50 °C, and the aqueous phase was separated. The organic phase was washed sequentialy with 100 mL water, 100 mL 5% aqueous sodium bicarbonate, and 100 mL water.The organic phase was transferred to a 1 L 3 neck flask equipped for mechanical stirring and distillation. The mixture (ca 400 mL) was distilled at atmospheric pressure until 150 mL of distillate had been collected.The head temperature reached 107 °C; the pot temperature

was 110 °C. The distillation was continued with continuous addition of n-propanol at such a rate as to maintain a constant volume (ca 350 mL) in the pot. The distillation was stopped when a total of 525 mL of n-PrOH had been added and a total of 800 mL of distillate had been collected. The temperature of both the head and pot rose from 94 °C to 98 °C during the solvent switch. Toluene and n-PrOH form an azeotrope boiling at 97.2 °C composed of 47.5% toluene and 52.5% n-PrOH. The mixture was allowed to cool gradually to 20 °C over 3h and aged for 12 h.
The mother liquor was found to contain 2% toluene and 4 mg/mL of sulfonamide. The solubility of the sulfonamide in various mixtures of toluene and n-PrOH has been determined by HPLC assay:

%toluene in n-PrOH	solubility of 1 in mg/mL
0	2.36
5	3.02
10	4.23
20	7.51
25	10.3

The crystalline slurry was filtered and washed with 3 x 100 mL of n-PrOH. The product was dried in a vacuum oven at 50 °C with a nitrogen bleed for 16 h to furnish 65.5g (82 % from aldehyde **5**) of **6** as a tan solid with 93.5 wt% purity.

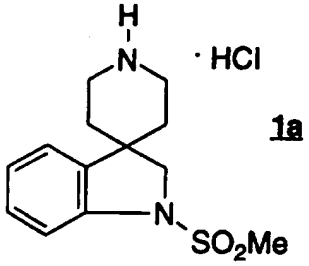
Typical HPLC profile of solid:

Area %	Identity
<0.1	CBZ-spiroindoline **9**
>99	CBZ-sulfonamide **1**
<1 tot..	other impurities (<0.2% ea.)

For additional purification, a 40.0 g sample of the n-PrOH crystallized sulfonamide was dissolved in 134 mL of EtOAc at 60 °C and treated with 8.0 g of Darco G-60 carbon for 1 h at 60 °C. After the addition of 2.0 g Solkafloc the slurry was filtered through a pad of 4.0 g Solkafloc, and the pad was washed with 90 mLof EtOAc at 60 °C.

Prior to the addition of the carbon the solution was a brown color. The filtration proceeded well without plugging to give a golden yellow filtrate. The filtrate was distilled at atmospheric pressure in a 500 mL flask (pot temperature 80-85 °C) until 100 g (100 mL) of residue remained. This solution was allowed to cool to 35 °C over 3 h. Over a 1 h period, 116 mL of cyclohexane was added with good agitation at 35 °C. The mixture was cooled to 20 °C over 1 h and aged at 20 °C for 12 h. At 35°C much of the sulfonamide has crystallized out and the mixture is thick. Addition of cyclohexane at 20 °C makes agitation difficult. After the age the supernatant was found to contain 2.5 mg **1**/g . The crystalline slurry was filtered and the cake was washed with 77 mL of 2:1 cyclohexane-EtOAc and 2 x 77 mL of cyclohexane. The product was dried in a vacuum oven at 50 °C with a nitrogen bleed for 16 h to furnish 34.2 g of **1** (MW = 400.3) as a white crystalline solid (85 % recovery from crude **1**, 70 % from **5** with >99.9 wt % purity).

EXAMPLE 8



1a

HCl Salt of Spiroindoline-methanesulfonamide (**1a**)

Materials:

CBZ-spiroindoline-methanesulfonamide	941 g (2.35 mol)
Pearlman's catalyst 20% $Pd(OH)_2/C$	188 g
THF	8 L
MeOH	7 L

The catalyst was suspended in 7 L of MeOH and transferred into the 5 gal autoclave followed by the solution of **8** in 8 L of THF. The

mixture was hydrogenolyzed at 25 °C at 80 psi of H_2. After 2.5 h the temperature was raised to 35 °C over 30 min.

HPLC analysis indicated complete consumption of Cbz-spiroindoline-methanesulfonamide. HPLC conditions: 25 cm Dupont Zorbax RXC8 column with 1.5 mL/min flow and detection at 254 nm. Gradient Schedule:

Time (min	0.1% aq. H_3PO_4:MeCN
0	70:30
3	70:30
12	20:80
25	20:80

retention times: Spiroindoline = 7.6 min,
Cbz-spiroindoline-methanesulfonamide = 13.6 min.

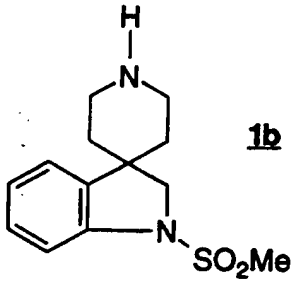
The mixture was purged with nitrogen and the catalyst was removed by filtration through Solka-floc while still warm. The catalyst was washed with 4 L of THF and 2 L of MeOH. The pale yellow filtrates were concentrated to a thick oil at 10 mbar and <25 °C. The solvent switch was completed by slowly bleeding in 15 L of EtOAc and reconcentrating to dryness. The residue solidified to a hard off-white mass. MeOH (1.5 L) was added and the mixture was heated to 70 °C to give a homogenous solution. While the solution was at 70 °C, 10.5 L of EtOAc at 20 °C was added. The temperature fell to 40 °C, and the mixture remained homogenous.

Subsequent experiments suggested that it is more convenient to solvent switch the MeOH-THF filtrates to MeOH, concentrate to the desired volume, and then add the EtOAc. This avoids the solidification of the residue upon concentration of the EtOAc solution.

Hydrogen chloride diluted with about an equal volume of nitrogen was passed into the solution. The temperature rose to 60 °C over the course of 15 min, and a white precipitate of the hydrochloride salt formed. Diluting the HCl with nitrogen only avoids the reaction mixture sucking back and may not be necessary.

The mixture was cooled in an ice bath, and the hydrogen chloride addition was continued for 1h. The temperature gradually fell to 20 °C. The suspension was aged for 2 h while the temperature was lowered to 10 °C. The crystalline product was isolated by filtration, and the filter cake was washed with 3 L of EtOAc. It was dried in the vacuum oven at 35 °C to give 1.18 kg (86%) of the title product **1a** as an off-white crystalline solid of >99.5 area % purity by HPLC analysis. HPLC conditions: 25 cm Dupont Zorbax RXC8 column with 1.5 mL/min flow and detection at 230 nm; isocratic 35% MeCN, 65% of 0.1% aqueous ammonium acetate. Retention time: **1a** = 5.4 min.

EXAMPLE 9



1b

Spiroindoline-methanesulfonamide (Free base form) (**1b**)

A 250 mL aliquot of the filtrate from the Cbz-hydrogenolysis containing 4.67 g of **1** (free base) was concentrated to ca 10 mL. The residue was dissolved in 20 mL of EtOAc and the solution was reconcentrated to ca 10 mL. This was repeated once more, and 10 mL of EtOAc was added to the residue. A crystalline precipitate began to form. MTBE (20 mL) was added in one portion. Additional crystalline solid precipitated, but the supernatent still contained a substantial quantity of dissolved product which did not precipitate on standing. Hexanes (70 mL) were added dropwise over 2 h to the mixture with vigorous stirring. The slow addition of the hexanes is neccessary to avoid the oiling out of the amine.

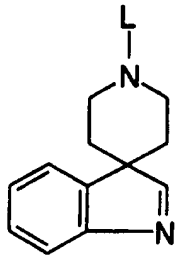
The agitated mixture was aged for 1h and filtered. The filter cake was washed 20 mL of 1:1 MTBE-hexanes and then with 20 mL of hexanes. The product was dried under a stream of nitrogen to give 3.86 g

(82%) of the free amine of **1b** as an off white crystalline solid of >99.5 area % purity. HPLC conditions: 25 cm Dupont Zorbax RXC8 column with 1.5 mL/min flow and detection at 230 nm; isocratic 35% MeCN, 65% of 0.1% aqueous ammonium acetate. Retention time: **1b** = 5.4 min.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, reaction conditions other than the particular conditions as set forth herein above may be applicable as a consequence of variations in the reagents or methodology to prepare the compounds from the processes of the invention indicated above. Likewise, the specific reactivity of starting materials may vary according to and depending upon the particular substituents present or the conditions of manufacture, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

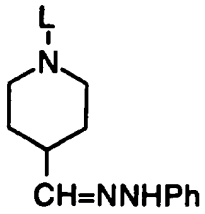
WHAT IS CLAIMED IS:

1. A process for the preparation of a compound of formula I:



I

wherein L is hydrogen or an amino protecting group, which comprises reacting a compound of the formula:



in the presence of a catalytic agent to give the compound of formula I.

2. The process of Claim 1 wherein the catalytic agent is selected from the group consisting of: trifluoroacetic acid; hydrogen fluoride; hyrogen chloride; hydrogen bromide; hydrogen iodide; chlorotrimethylsilane; trifluoromethanesulfonic acid; methanesulfonic acid; camphorsulfonic acid; sulfuric acid; phosphoric acid; benzenesulfonic acid; p-toluenesulfonic acid; and p-chlorobenzenesulfonic acid.

3. The process of Claim 1 wherein the catalytic agent is selected from the group consisting of: trifluoroacetic acid; methanesulfonic acid; camphorsulfonic acid; benzenesulfonic acid, p-toluenesulfonic acid; and p-chlorobenzenesulfonic acid.

4. The process of Claim 1 wherein the catalytic agent is trifluoroacetic acid.

5. The process of Claim 1 wherein the solvent is selected from the group consisting of: acetonitrile; propionitrile; chlorinated hydrocarbons selected from dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, and ortho-dichlorobenzene; benzene; toluene; xylenes; and mixtures thereof.

6. The process of Claim 1 wherein the solvent is selected from the group consisting of: dichloromethane; chloroform; mixtures of toluene-acetonitrile (4:1 to 100:1 v/v); mixtures of chlorobenzene-acetonitrile (4:1 to 100:1 v/v); and mixtures of ortho-dichlorobenzene-acetonitrile (4:1 to 100:1 v/v).

7. The process of Claim 1 wherein the solvent is selected from the group consisting of: dichloromethane; mixturesof toluene-acetonitrile (9:1 to 100:1 v/v); mixtures of chlorobenzene-acetonitrile (9:1 to 100:1 v/v); and mixtures of ortho-dichlorobenzene-acetonitrile (4:1 to 100:1 v/v).

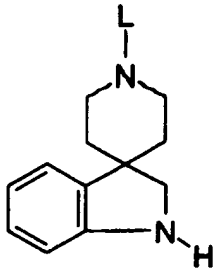
8. The process of Claim 1 wherein the temperature of the reaction is between -40 and 150°C.

9. The process of Claim 1 wherein the temperature of the reaction is between 35 and 55°C.

10. The process of Claim 1 wherein the compound of formula I, L is selected from: benzyloxycarbonyl; 2-chlorobenzyloxycarbonyl; 4-methoxybenzyloxycarbonyl; and 4-nitrobenzyloxycarbonyl.

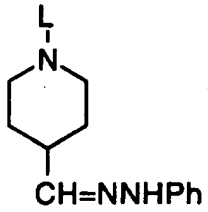
11. The process of Claim 1 wherein the compound of formula I, L is benzyloxycarbonyl.

12. A process for the preparation of a compound of the formula II:

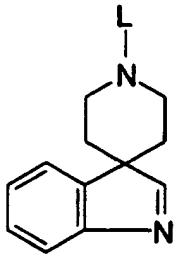


II

wherein L is hydrogen or an amino protecting group, which comprises reacting a compound of the formula:



in the presence of a catalytic agent, to give a compound of the formula I:



I

followed by the reaction of the compound of formula I with a reducing agent to give the compound of formula II.

13. The process of Claim 12 wherein the compound of formula I is reacted *in situ* with a reducing agent to give the compound of formula II.

14. The process of Claim 12 wherein the reducing agent is selected from the group consisting of: sodium borohydride, lithium borohydride, lithium aluminum hydride, di-isobutylaluminum hydride, bis(2-methoxyethoxy)aluminum hydride, triacetoxy borohydride, and borane or carboxylates thereof.

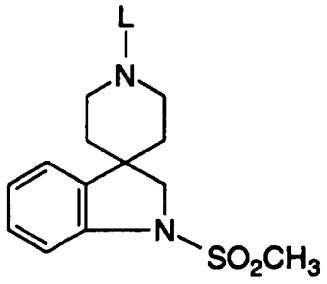
15. The process of Claim 12, wherein the reducing agent is selected from the group consisting of: sodium borohydride, and lithium borohydride.

16. The process of Claim 15, wherein the reaction of the compound of formula I is conducted in the presence of an alcohol.

17. The process of Claim 16, wherein the alcohol is selected from the group consisting of: methanol, ethanol, and isopropanol.

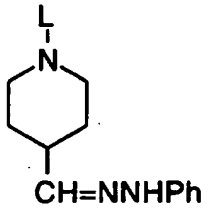
18. The process of Claim 16, wherein the alcohol is methanol.

19. A process for the preparation of a compound of the formula III:

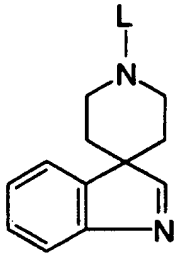


III

wherein L is hydrogen or an amino protecting group, which comprises reacting a compound of the formula:

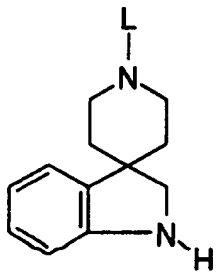


wherein L is hydrogen or an amino protecting group,
in the presence of a catalytic agent, to give a compound of the formula I:



I

wherein L is hydrogen or an amino protecting group, followed by the reaction of the compound of formula I with a reducing agent to give a compound of formula II:



II

wherein L is hydrogen or an amino protecting group, followed by the reaction of the compound of formula II with a sulfonylating agent to give the compound of formula III.

20. The process of Claim 19 wherein the sulfonylating agent is selected from the group consisting of: methanesulfonyl chloride, methanesulfonic anhydride, and methanesulfonic acid in the presence of a suitable dehydrating agent.

21. The process of Claim 19 wherein the sulfonylating agent is selected from the group consisting of: methanesulfonyl chloride, and methanesulfonic anhydride.

22. The process of Claim 19 wherein the sulfonylating agent is methanesulfonyl chloride.

23. The process of Claim 19 wherein the reaction of the compound of formula II is conducted in the presence of an amine base.

24. The process of Claim 23 wherein the amine base is selected from the group consisting of: di-isopropylethylamine, triethylamine, dimethylaminopyridine, and 1,8-diazabicyclo[5.4.0]undec-7-ene.

25. The process of Claim 23 wherein the amine base is di-isopropylethylamine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/05259

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C 07 D 401/04
US CL : 546/17
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/17

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO, A, 94/29309 (MERCK & CO., INC.) 22 December 1994, see entire document, especially pages 17, 48-55.	1-25

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 30 MAY 1996	Date of mailing of the international search report 15 JUL 1996
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